

THE BRITISH JOURNAL OF VENEREAL DISEASES

started great efforts had been made to encourage local authorities to increase their facilities, and they had been accompanied by an offer of 75 per cent. of the expense of any such increased facilities. This situation had been watched very carefully, and local authorities had been regularly written to with requests that they would again consider the question of increasing the facilities. It would be astonishing to those present, if they looked at the records, to find how comparatively free from infection, as judged by the localities of infections of Service men, were the areas which were "backward" in respect of facilities.

Much had also been said about certain areas having inconveniently placed facilities which could not be made use of by women at work. He had looked into this matter and had got reports from medical officers of health. There was no denying that there were a number of bad cases, but a sense of proportion must be kept in this matter, and credit must be given to those concerned for carefully looking into the question from the local point of view. He was certain that the scheme for V.D. treatment was not as defective as suggested by certain speakers that afternoon, and he thought this country had got as good a scheme as any other.

As to notification, it must be agreed that notification was a "wash-out" so far as private practitioners were concerned. American records showed that only a small proportion of the private cases discovered by their censuses had been reported by private practitioners.

He joined issue with Major Laird on his comparison of Liverpool with Stockholm. Liverpool, for example, was nearer to South America than Stockholm was. The incidence of V.D. among seamen in ships trading with South America was far higher than among seamen in ships not touching that continent.

As for education in Sweden, when he and others were over there reporting on the Swedish system, they tried to discover what the man in the street thought about it. As far as they could gather, he did not seem to know much about the laws and regulations. But there was a far more realistic attitude on such matters in Sweden than we had here, and less false shame. For example, in a male clinic there were women nurses and he had seen a man irrigated by one of these.

Major LAIRD, in reply, said that he thought they all saw eye to eye in principle, with divergencies in detail. He had prefaced his plea for further powers by insisting on further education of medical practitioners. He wanted the voluntary method to be retained and to be as good as it could be, but he wanted also the power to deal with people with whom the voluntary system failed.

At the end of the meeting the following resolution was put to the large audience of members and was passed by an overwhelming majority:—

"That in the opinion of this meeting of the Medical Society for the Study of Venereal Diseases, further powers, legislative and administrative, in the treatment and prevention of venereal diseases are required to deal with sources of infection, contacts and defaulters."

V

SOME ASPECTS OF THE SEROLOGY OF SYPHILIS, WITH SPECIAL REFERENCE TO ITS THEORETICAL AND PRACTICAL SIGNIFICANCE *

By H. SACHS, M.D. (from the Department of Bacteriology, School of Pathology, Trinity College, Dublin).

THE problem whether the serological syphilis tests have an unequivocal diagnostic and therapeutic significance or if falsely positive results may also be obtained is recently again the object of discussion.

* With partial use of the writer's article "The Wassermann Reaction, etc." in the *Irish Journ. of Med. Science*, February, 1941.

SOME ASPECTS OF THE SEROLOGY OF SYPHILIS

Those who remember the early days of the Wassermann reaction know that at that time many non-specific reactions were observed, particularly in pregnancy, cancer, tuberculosis, gonorrhœa and other diseases. In the meantime, however, the syphilis tests have been improved considerably, but their sensitivity has been increased more and more. In spite of all technical improvements has the unlimited deliberate increase of their sensitivity been achieved without endangering the characteristic behaviour of the tests? In answering, it is useful to recollect the development of the serology of syphilis and to be aware of the character of the syphilitic blood alteration as well as of the blood alterations which may occur under certain conditions independently of syphilitic infection.

I

When Wassermann (together with A. Neisser and Bruck) discovered in 1906 the alteration of the blood characteristic of syphilis, the procedure (shortly called "Wassermann reaction") and the result seemed to correspond with the antibody reactions known hitherto. The reagent used was an extract from tissues rich in spirochætes, and the complement fixation test which was devised had proved very suitable for the detection of antigen-antibody reactions in general. Thus the conclusion that antibodies specifically directed against the pathogenic agent (*Spirochæta pallida*) are responsible for a positive Wassermann reaction appeared completely justifiable. Nevertheless this reaction was distinguished from other serological tests used before by the fact that tissue extracts were the antigens. Such extracts, when originating from tissues rich in spirochætes, certainly contain spirochætal antigens, but it must be emphasised that spirochætal antigens are by no means their only constituents. There is no doubt that the normal components of the tissues also are present, and it could be asked from the first whether they play any part in the reactivity observed. This question was answered by two unexpected observations. The first showed that the active principle present in the tissue extracts is soluble in alcohol. The second demonstrated the fact that extracts from tissues of non-syphilitic human beings or even of animals may also be used to attain the same results as on using extracts from syphilitic tissues, provided that the extraction is performed by using alcohol instead of water or saline. Those who were inclined to follow the antibody theory of the Wassermann reaction encountered a perfectly new and at that time revolutionary aspect. They were obliged to assume that antigens may be soluble in alcohol, whereas only proteins had previously been believed to be antigenic. Since, furthermore, the Wassermann reaction could be performed without using any spirochætal material, the antigens could not originate from *Spirochæta pallida*. Hence only two possible explanations seemed to be available if antibody formation was considered responsible for the characteristic blood alteration in syphilis.

(1) Antibody formation could be caused by the immunising action of the spirochætes; then the spirochætal antigen apparently was not only present in the spirochætes but everywhere in the tissues of man and animals.

(2) Antibody formation could be the consequence of auto-

THE BRITISH JOURNAL OF VENEREAL DISEASES

immunisation, the constituents of the tissues being the immunising antigens set free in the diseased body and not restricted to man.

All experiments, however, to show that the tissue extracts used for the Wassermann reaction are antigens failed. On immunising rabbits with alcoholic extracts no distinct alteration of the blood serum could be observed. Thus many workers were prompted to consider the special qualities of the serum in syphilis to be due to a peculiar colloidal alteration and not to antibody formation. On this reasoning many precipitation tests were tried and even recommended. They were all based on the flocculation of serum globulins, the most simple of them being dilution of serum with distilled water (so-called "Klausner reaction"). Such reactions were often published with more or less enthusiasm, but they soon proved quite unsuitable for the differentiation of syphilitic sera. Thus no theory was able to cover the observations available at that time, and the nature of the blood alteration in syphilis remained obscure.

II

Independently of the development of the Wassermann reaction another phenomenon was observed, the analysis of which revealed striking similarities. This was the discovery of the heterogenetic antigen by Forssman in 1911. When rabbits are immunised with guinea-pig tissue suspensions, the antibodies produced act not only on the homologous antigen, but also cause hæmolysis of sheep or goat red cells, just in the same strength as do the usual immune sera against sheep or goat blood. The antigen responsible for the formation of heterogenetic anti-bodies is, therefore, not restricted to a certain or to related species but is widespread in living organisms. It is present in guinea-pig, horse and other animals, but missing in rabbit, ox, pig, etc. The difference in comparison with the Wassermann antigen is shown only by the fact that the heterogenetic antigen is restricted to certain (though many) species while the Wassermann antigen is ubiquitous in nature. Both actually are heterogenetic, their distribution being only of different degree. Similarities between the heterogenetic and the Wassermann antigen became evident also from other observations. The heterogenetic antigen proved soluble in alcohol, but the alcoholic extract reacted only *in vitro* with heterogenetic antibodies (by complement fixation or flocculation), not producing antibody formation in rabbits. The conditions which rule the interaction between alcoholic extracts and heterogenetic immune serum are, however, clear, for the latter contains beyond doubt antibodies produced by immunisation with suspensions of heterogenetic tissues in saline. The curious fact was that components soluble in alcohol behaved as antigens when examined by *in vitro* tests but failed to act as immunising agents. This discrepancy was definitely elucidated by the work of Landsteiner (1921-23) which confirmed the facts mentioned above and showed that nevertheless heterogenetic antibodies develop in the body on immunisation with mixtures of alcoholic extracts from heterogenetic tissues and foreign protein, *e.g.*, pig serum. Of course, two different antibodies are produced in such a way, one against the foreign protein component, the other against the heterogenetic antigen present in the alcoholic extract. Actually the latter is not a full

SOME ASPECTS OF THE SEROLOGY OF SYPHILIS

antigen because it reacts by itself only *in vitro* with the corresponding antibodies. It acquires, however, immunising action *in vivo* in combination with a proteinic antigen. The alcoholic extract only contains fractions of the antigen, which were designated "haptens" by Landsteiner. The "combination-immunisation" is a suitable method of proving the hapten character of reagents which give complement fixation or flocculation without causing antibody formation *in vivo*.

As regards the Wassermann reaction, the origin and character of the reagins present in the blood serum were indeed unknown. This is the essential difference in comparison with the heterogenetic antigen-antibody reaction. On account of the parallelism between both reactions and the discovery of the combination-immunisation it could be assumed that the components of the extracts used in the Wassermann reaction are also haptens. This supposition, however, appeared at first unlikely because the active constituents are ubiquitous in nature. If it was correct, the antibodies in syphilis were to be considered as auto-antibodies. Experiments were carried out, however, by the writer to decide the question (together with A. Klopstock and Weil) in 1925. Rabbits were immunised with mixtures of alcoholic extracts from rabbit tissues and pig serum. Only on immunisation with such mixtures—not with the single components or by their injection separately—were antibodies against alcoholic tissue extracts produced. The serum obtained in such a way showed an alteration corresponding in every respect with that in syphilis; thus a real Wassermann reaction and also flocculation reactions developed without syphilis. The presence of haptens in alcoholic extracts obtained from any tissues, not only those originating from heterogenetic species was proved by these experiments. At the same time the only fact which was missing to support the antibody theory of the blood alteration in syphilis had been supplied. There was no longer any reason to doubt the antibody character of the reagins in syphilitic sera.

III

In spite of this progress in the knowledge of the Wassermann reaction the question remained whether the antibodies are produced by the immunising action of the spirochætes or whether they are the consequence of an auto-immunisation of the diseased body against its proper components set free by the syphilitic infection. The experiments mentioned above allow the assumption of such a mechanism. It must be borne in mind, however, that in following this assumption spirochætal antibodies also must be produced because only spirochætal components can be the foreign proteinic part which is necessary for combination-immunisation. On the other hand, F. Klopstock has pointed out that rabbits may produce a positive Wassermann reaction on immunisation with spirochætes. It is not clear whether such spirochætal antisera correspond with those obtained by immunisation with mixtures of alcoholic tissue extracts and foreign protein. In any case they usually react more strongly with suspensions or extracts of spirochætes than with tissue extracts such as are used for the Wassermann reaction. Moreover, the serum of rabbits immunised with killed spirochætes differs from that of animals infected with syphilitic tissues. It may be that this difference is caused by the fact that the

THE BRITISH JOURNAL OF VENEREAL DISEASES

spirochætes cultured *in vitro* which are used for immunisation are probably not *Spirochæta pallida* as it is still doubtful if cultures of this micro-organism have been obtained. On the other hand, it must be emphasised that *Spirochæta pallida* and other spirochætes may contain the same antigens to a greater or less degree, so that a reactivity of the serum with spirochætal antigens would not be surprising in syphilis even if the antigens did not originate from the true *Spirochæta pallida*.

Actually serological syphilis tests have also been performed with spirochætal antigens, since Gæhtgens has recommended such a reagent, called "Palligen," for diagnostic use. Many workers are very satisfied with these "Pallida" preparations. The statements in the literature yield, however, some contradictions. I would refer only to some papers published recently. Beck as well as Eagle and Hogan have confirmed the high sensitivity of the Pallida-reaction in serological syphilis tests. They also showed—in agreement with Gæhtgens—that the absorption of syphilitic sera with tissue extracts usually removed their reactivity with these reagents, but not that with spirochætal preparations. On the other hand, Beck usually found abolition of the reactivity of syphilitic sera only with spirochætes when the latter were used for absorption, while Eagle and Hogan claimed that by the same procedure all reactivity—with tissue extracts and with spirochætes—disappears. Kolmer, Kast and Lynch recently pointed out, like Beck, that absorption with spirochætes removes only antibodies which react with spirochætal antigens but not those which are concerned in the Wassermann and flocculation tests. The statements of Eagle and Hogan may require, therefore, further confirmation. It is noteworthy that Eagle and Hogan obtained antibodies against spirochætes as well as a positive Wassermann reaction in rabbits on immunisation with mixtures of tissue extracts and syphilitic serum. This result would suggest the supposition that spirochætes and mammalian tissues contain common partial antigens. On the other hand, it may be questionable whether the production of spirochætal antibodies on immunisation with tissue extracts in combination with human serum as reported by Eagle and Hogan might be the consequence of a non-specific increase of natural antibodies against spirochætes. It is interesting to note that Kolmer and his associates do not assume any relation between the specific spirochætal antibody and the reagin responsible for the usual syphilis tests. If those who believe that the spirochætes are the immunising agent are right, this would mean a return to the original conception of Wassermann whose earliest theory assumed that spirochætal antibodies are detected by the Wassermann reaction. The difference would remain only in the fact that these antibodies are not species-specific but heterogenetic in so far as they also react with components which are present in or may be extracted from all tissues.

Although many authors follow to-day this explanation, it must be realised that it is not proved with sufficient certainty. Apart from the question whether the cultured spirochætes used are really *Treponema pallidum* (which does not seem to be of decisive significance as mentioned above) it may be remembered that spirochætes are cultured in media containing mammalian components, that the antisera pro-

SOME ASPECTS OF THE SEROLOGY OF SYPHILIS

duced by immunisation with killed spirochætes usually behave otherwise than the sera of infected syphilitic rabbits, while the qualities of the latter correspond with those of immune sera obtained by combination-immunisation. Finally the spirochætal suspensions used for serodiagnostic work contain phenol which also intensifies the reactivity of tissue extracts in the Wassermann reaction, as has been known for some time, and even may be able to set free masked antigens. It is questionable, therefore, how far phenol influences the sensitivity of complement fixation tests with spirochætal antigens. On the other hand, Kolmer and his associates recently pointed out, in contrast with other statements, that spirochætal antigens are inferior to cholesterolised tissue extracts because of the higher percentage of non-specific reactions, while they are inferior with regard to sensitivity when sufficiently diluted.

Thus the question by what mechanism the antibodies in syphilis develop cannot apparently be answered at present. The theory according to which the formation of these antibodies is the consequence of auto-immunisation seems to cover the observations just as well as does the spirochætal antibody theory. Such a theory requires the assumption of a liberation of originally masked haptens in the diseased tissues by the action of spirochætes. Accordingly spirochætal antibodies also must be produced because evidence is at hand that, by such a procedure of combination-immunisation, antibodies against both components must develop. In any case the fact must be stressed that the reagins in the syphilitic blood serum are antibodies. This has been proved by the demonstration that alcoholic tissue extracts which are the reagent for the Wassermann and flocculation tests actually contain haptens.

IV

In these circumstances the question arises as to whether antibodies only are responsible for complement fixation and flocculation following the interaction between serum and tissue extracts or other reagents. Although opinions in this respect may differ even to-day it is unquestionable that another mechanism of serological reactivity exists, apart from that caused by antibody action. It has been known for a long time that animal sera can give positive Wassermann and flocculation tests more or less frequently when the technique for the serodiagnosis of syphilis in man is used. Rabbit serum behaves in this way. When the alteration of the rabbit serum caused by the injection of alcoholic tissue extract and foreign protein was discovered many critics believed that the result was only the consequence of an increase of the non-specific serological reactivity. The sera obtained in this way have, however, the character of immune sera in every respect. They are not only distinguished by their high titre, but their active components may be regained at higher temperature from the complexes into which they enter with alcoholic tissue extracts. Such an elution, as was demonstrated by Witebsky, is characteristic of antibodies in general. Moreover, the non-specific reactivity of rabbit serum is avoidable when weaker tissue extracts are used, particularly when they are less cholesterolised than those utilised in the syphilis tests with human

THE BRITISH JOURNAL OF VENEREAL DISEASES

serum. The fact that cholesterolised extracts suitable for the serodiagnosis of syphilis in man are enabled to react with rabbit and other animal sera to a certain degree is accounted for by the hydrophobe character which the extract dilutions acquire by the addition of cholesterol. The reactivity induced in this way, however, may be quite different from a real antibody reaction. It is caused by colloidal qualities dependent on the behaviour of the serum proteins and their colloidal structure. It is fortunate that the serum of healthy people is relatively stable, so that non-specific positive results may be rather easily avoided on using suitable extracts for the syphilis tests. Any alteration, however, of the normal serological composition such as occurs in pregnancy as well as in many diseases, *e.g.*, cancer, tuberculosis and other infections, as also in pathological conditions such as anæmia, cirrhosis of the liver, etc. may result in a pathological reactivity akin to that of animal sera. Such a knowledge already followed from the early experiences learnt by the Wassermann reaction when many falsely positive results were reported in pregnancy, cancer, tuberculosis and infectious diseases. These are just those very conditions or diseases in which the sedimentation rate of the blood is increased. The sedimentation rate, as is well known, is dependent on the fibrinogen content of the plasma. The plasma of blood samples with a high sedimentation rate also shows an increased precipitability caused by different agents which precipitate slightly the proteins. One speaks, therefore, of an increased lability of the plasma proteins, independently of the question whether this concerns an increase of the more easily precipitable components or an alteration of their colloidal behaviour. While the fibrinogen does not play any part on using serum the serum proteins also may be altered in such cases quantitatively or qualitatively. The globulin : albumin ratio may be greater or the globulins may have a colloidal structure responsible for their greater precipitability. In any case such "labile" sera are more easily precipitated by different influences which particularly concern the most labile components of the euglobulin fraction.

The reagents (tissue extracts, etc.) used for the serological syphilis tests are able also to react with the proteins of labile sera. The results of such an interaction are just the same as in true antibody reactions, complement fixation or flocculation. The difference is due only to the fact that in these circumstances the extract components react immediately with the serum globulins while the specific reaction between antibody and antigen (or hapten) is secondarily followed by the same alterations inducing complement fixation or flocculation. This consideration makes non-specific reactions in the serodiagnosis of syphilis understandable. It must be realised that the extracts used as "antigens" are not at all pure reagents. The specific component responsible for the antibody reaction is only a small share (chemically not sufficiently recognisable) which adheres to a big portion of ballast material originating from the tissues. This ballast material and its colloidal structure is of great importance because it may act like antigens—so to speak as "pseudo-antigens"—but only because of its colloidal behaviour. The result is a non-specific reaction which will occur the more easily the more labile the serum globulins. One has called such non-specific reactions, therefore, "lability reactions."

SOME ASPECTS OF THE SEROLOGY OF SYPHILIS

V

The terms "lability" and "lability reactions" appear justifiable by the fact that such lability reactions as are responsible for non-specific complement fixation or flocculation are often associated with an easier precipitability of serum by common reagents precipitating proteins. Another explanation, however, which has been evolved assumes that non-specific reactions may be caused by antibodies related to those developing in syphilis, or caused by symptomless infections. Such antibodies may be induced by the immunising action of other micro-organisms or by decay of tissues similar to that in syphilis, but not restricted to this disease. Although it is true that antibodies identical with those characteristic of syphilis may be produced in some other infectious diseases, such as yaws, malaria, leprosy, subacute bacterial endocarditis, etc., I do not believe that the theory which endeavours to explain non-specific reactions in general by the same mechanism as is responsible for the Wassermann reaction is correct. First of all it must be emphasised that non-specific reactions are more frequent and stronger when unheated serum is used instead of heated serum. Heating the serum, first recommended for the intensification of the Wassermann reaction on account of the destruction of the complement activity, just weakens the reactivity and increases at the same time the specificity. An unheated serum of a pregnant non-syphilitic woman, *e.g.*, may give a stronger complement fixation than a heated syphilitic serum, while the reactivity disappears completely after heating. On this account heating the sera at 55° C. for half an hour is one of the most important measures to warrant the reliability of nearly all serological syphilis tests. In flocculation tests moreover, the sensitivity is increased in such a way. Only when a more concentrated sodium chloride solution is used as medium, as in Meinicke's clarification test, may unheated serum be used. The higher salt concentration prevents the reactivity of labile globulins and acts, therefore, in the same manner as heating which causes their stabilisation.

Apart from the importance of heating the serum, the temperature at which flocculation tests are performed is of paramount importance. Observations in this respect have been already presented as early as the first Meinicke flocculation reactions and the Sachs-Georgi reaction were introduced. Particularly on using the Sachs-Georgi reaction it was pointed out that non-specific reactions which occur at room temperature or in the refrigerator may disappear after a short stay in the incubator. The interference of this so-called "thermolabile flocculation" was the reason for keeping the tubes in the incubator for a longer period before reading the results. On the other hand, it was recognised already at this time that the sensitivity of the specific flocculation decreases in the cold, a fact which applies also to the heterogenetic flocculation and speaks again in favour of the antibody character of the syphilitic blood alteration. It is interesting to note that recently Kahn also observed these two types of reactivity on using the Kahn test. According to his work the "syphilitic type" is distinguished by the fact that flocculation is more marked at 37° C. than at 1° C., while the "general biological type" (non-specific

THE BRITISH JOURNAL OF VENEREAL DISEASES

reactivity) is characterised by stronger flocculation at 1° C. than at 37° C. Kahn has recommended the performance of the flocculation test in the warmth and in the cold as a "verification test" in doubtful cases. There may be hardly any doubt that Kahn's syphilitic type corresponds with the antibody reaction, while the "general biological type" reflects the non-specific reactions designated as "lability reactions" above. Thus the verification test may be indeed of diagnostic value in questionable cases, as is the elution of antibodies at higher temperature proposed by Witebsky as a confirmatory reaction.

It may be justifiable to assume a general biological mechanism for the lability reactions. Actually it is possible to obtain with nearly all sera a positive Wassermann reaction, either if the sera are unheated or if the salt concentration is diminished. Both are understandable, the unheated serum yielding a sufficient lability, the diminution of the salt content facilitating the reactivity of the labile serum globulins. In recent experiments which are in progress I observed together with Dr. Havelock Nelson that in certain circumstances on using hyper-sensitive extract dilutions flocculation may be obtained with all sera at room temperature, but that after a subsequent stay in the incubator only flocculations produced by syphilitic serum remain while the others dissolve. This shows that a certain degree of non-specific reactivity may be present in every serum.

VI

On summarising it must be taken into consideration that two types of reactivity are possible:

- (1) Antibody reactions (syphilitic type).
- (2) Lability reactions (general biological type).

Complement fixation and flocculation are the consequence of the same alteration of globulins which may be caused either specifically and indirectly by antibody action or non-specifically and directly by serum lability. Although the flocculation tests are usually more sensitive than the Wassermann reaction, occasionally the opposite result may be obtained. The reason for this is that complement fixation occurs best when the antigen-antibody complexes are in the stage of development and sometimes because of the dependence on optimum proportions just in the circumstances that do not induce a visible flocculation. On the other hand, complement fixation may be inhibited by the non-specific components of the serum. Such an influence may cause a negative Wassermann reaction while flocculation is positive, although complement fixation is more sensitive in principle. Moreover, under suitable conditions the Wassermann reaction is most specific. Because of these peculiarities, both complement fixation and flocculation must be used if the true evaluation of a suspected syphilitic serum is desired.

In any case care must be taken to follow the technique strictly according to the directions of the author of the method. The reason for this is that the colloidal qualities of the extract dilution are of outstanding significance. The sensitivity of antibody reactions against haptens present in dilutions of alcoholic extracts is mainly dependent on the colloidal behaviour of the latter. They must have

SOME ASPECTS OF THE SEROLOGY OF SYPHILIS

sufficiently coarse and hydrophobe qualities. These are attained by addition of cholesterol or, in the clarification tests, of resin, and by a suitable method of dilution with 0.9 per cent. or more concentrated sodium chloride solution. Extract dilutions of the same chemical composition as those of greatest sensitivity may fail to react if the suitable colloidal (hydrophobe) character is not attained. Unfortunately the same influences which increase in such a way the sensitivity of antibody reactions also increase the non-specific reactivity, which only depends on the colloidal structure of the extract dilutions, while the latter favours the secondary stages of antibody reactions necessary for their visibility. It is only a question of experience to find out the most suitable conditions that display the greatest sensitivity within those limits which avoid non-specific reactivity as much as possible. Hence routine work requires strictest attention to the prescriptions and rules laid down for any test.

The ideal from the theoretical point of view, namely, highest sensitivity without any non-specific reactivity, will never be reached. One must be satisfied with a compromise, combining sufficiently high sensitivity with restriction of non-specific reactions to a minimum. The requirement of verification tests, as is evident recently, seems to show that at least some syphilis tests are at present too sensitive. This concerns more the flocculation tests than the Wassermann reaction although the latter also may be unreliable when imperfectly performed. Those who believe that the antibodies in syphilis are induced by the immunising action of spirochætes are inclined to assume that many other pathogenic agents may dispose of the same heterogenous antigens and in such a way be responsible for non-specific reactions. There is, however, no doubt that the majority of non-specific or biologically false reactions are caused by another mechanism and are mostly avoidable. It is true that heating means a stabilisation of the serum, but it must be taken into consideration that this is a gradual and not an absolute alteration. If, therefore, the serum lability is increased as in pregnancy, cancer, infectious diseases, etc. heated serum also may be able to give lability reactions, the frequency and degree of which depend at the same time on the reagents used and on other details of technique.

VII

It would be a rather difficult task to enumerate all conditions which may possibly cause an increase of lability and thus induce non-specific reactions. This may happen more or less transitorily, apart from pregnancy, under the influence of many diseases and also after vaccination or serotherapeutic injections. Older and recent statements in the literature would yield a rather large list of possible sources of error. The fact may be stressed, however, that positive results in other diseases than in syphilis and in pregnancy are very exceptional if all care is taken in performing the tests and in avoiding a too extreme sensitivity. But it must be realised that the tendency prevails to get a high sensitivity in syphilis tests and to underrate the danger of non-specific reactivity.

The suitable choice of sera as controls in diagnostic routine work and in the evaluation of serum tests is, therefore, of greatest import-

THE BRITISH JOURNAL OF VENEREAL DISEASES

ance. Serum of pregnant women is most convenient to detect doubtful reliability. For this reason at least close co-operation between the physician and the serologist is absolutely desirable. The serologist should have short clinical records with regard to syphilis and to other diseases or pregnancy. Otherwise he works to a certain degree "in the dark" and will not be able to recognise when his tests are not correctly adjusted. The physician also should be aware of this situation and of the advantage of co-operation. He should not hesitate to inform the serological laboratory of the clinical diagnosis and the peculiarities of his case. Since an increase of lability may exist only for a limited period in some infectious diseases or in other conditions, in doubtful cases, it is desirable to repeat the examination of the blood at due intervals and to rely on the positive result only if it is continual. It should be realised that non-specific reactivity may result at present from another reason as in the early days of the Wassermann reaction. At the beginning the test was performed quite empirically without any knowledge of the peculiarities to be considered. To-day, however, the endeavour to increase the sensitivity is attended by a danger of passing the border-line which limits the reactivity characteristic of syphilis.

In any case it is of the greatest significance to know the two possibilities of serological reactivity, one (the syphilitic type) caused by antibody action, the other (general biological type) dependent on non-specific blood alterations. Both may induce the same result (complement fixation or flocculation, in serological syphilis tests. Their differentiation is the most important progress in the knowledge of the serology of syphilis. Only the due consideration of these two mechanisms independently of one another may guarantee the correctness of serological work and its practical application.

My thanks are due to the Medical Research Council of Ireland for the grant which has enabled me to continue my work. I am very grateful also for the hospitality of the School of Pathology, Trinity College, and for the facilities afforded by Professor O'Meara in the Department of Bacteriology.

VI

NON-GONOCOCCAL URETHRITIS *

By WING-COMMANDER G. L. M. McELLIGOTT

My contribution to this discussion is not so much to shed any fresh light on a condition of so mixed an ætiology as non-gonococcal urethritis, as to stimulate discussion on the subject, so that by the ventilation of our pooled experience there may emerge some degree of uniformity of opinion as to what are the most efficient and expeditious methods of treatment for this all too common condition.

In 1932 Harkness read a paper before this society on this very subject which was subsequently published in this Journal in March,

* An address delivered to the Medical Society for the Study of Venereal Diseases, May 30th, 1942.